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Long-term exposure to low levels of air pollution and mortality adjusting for road traffic noise: A Danish Nurse Cohort study

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ABSTRACT

Background: The association between air pollution and mortality is well established, yet some uncertainties remain: there are few studies that account for road traffic noise exposure or that consider in detail the shape of the exposure–response function for cause-specific mortality outcomes, especially at low-levels of exposure.

Objectives: We examined the association between long-term exposure to particulate matter [(PM) with a diameter of $< 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), $< 10 \mu\text{m}$ (PM_{10})], and nitrogen dioxide (NO_2) and total and cause-specific mortality, accounting for road traffic noise.

Methods: We used data on 24,541 females (age > 44 years) from the Danish Nurse Cohort, who were recruited in 1993 or 1999, and linked to the Danish Causes of Death Register for follow-up on date of death and its cause, until the end of 2013. Annual mean concentrations of $\text{PM}_{2.5}$, PM_{10} , and NO_2 at the participants' residences since 1990 were estimated using the Danish DEHM/UBM/AirGIS dispersion model, and annual mean road traffic noise levels (L_{den}) were estimated using the Nord2000 model. We examined associations between the three-year running mean of $\text{PM}_{2.5}$, PM_{10} , and NO_2 with total and cause-specific mortality by using time-varying Cox Regression models, adjusting for individual characteristics and residential road traffic noise.

Results: During the study period, 3,708 nurses died: 843 from cardiovascular disease (CVD), 310 from respiratory disease (RD), and 64 from diabetes. In the fully adjusted models, including road traffic noise, we detected associations of three-year running mean of $\text{PM}_{2.5}$ with total (hazard ratio; 95% confidence interval: 1.06; 1.01–1.11), CVD (1.14; 1.03–1.26), and diabetes mortality (1.41; 1.05–1.90), per interquartile range of $4.39 \mu\text{g}/\text{m}^3$. In a subset of the cohort exposed to $\text{PM}_{2.5} < 20 \mu\text{g}/\text{m}^3$, we found even stronger association with total (1.19; 1.11–1.27), CVD

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(1.27; 1.01–1.46), RD (1.27; 1.00–1.60), and diabetes mortality (1.44; 0.83–2.48). We found similar associations with PM_{10} and none with NO_2 . All associations were robust to adjustment for road traffic noise.

Discussion: Long-term exposure to low-levels of $PM_{2.5}$ and PM_{10} is associated with total mortality, and mortality from CVD, RD, and diabetes. Associations were even stronger at the $PM_{2.5}$ levels below EU limit values and were independent of road traffic noise.

1. Introduction

Outdoor air pollution is a ubiquitous exposure with numerous adverse health effects. Evidence on long-term exposure to air pollution and mortality is substantial, and the majority of studies are based on low-exposure settings in Western Europe (Beelen et al., 2014a) and North-America (Crouse et al., 2012; Di et al., 2017; Pappin et al., 2019; Villeneuve et al., 2015), with mean particulate matter with a diameter of $< 2.5 \mu m$ ($PM_{2.5}$) levels generally around or below limit values of 25 and $12 \mu g/m^3$, for European Union and United States, respectively (Liu et al., 2019). Still, there are uncertainties about the shape of exposure–response function of the association between air pollution and mortality below current air pollution limit values, important for future policy evaluations. Another research gaps remain as well, including lack of studies on air pollution and cause-specific mortality other than cardiorespiratory diseases, and lack of adjustment for noise among others.

The Global Burden of Disease (GBD) Study attributed 4.2 million deaths worldwide to $PM_{2.5}$, due to five specific causes including ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), lower respiratory infections, and lung cancer (Cohen et al., 2017). More recently, the Global Exposure Mortality Model (GEMM) attributed 8.9 million deaths to $PM_{2.5}$, in a new approach that included all-cause mortality, stating that air pollution effects would likely extend beyond the five causes of death from the GBD approach (Burnett et al., 2018). However, epidemiological studies on long-term exposure to $PM_{2.5}$ and mortality have typically focused on all-cause and cardiovascular disease (CVD) mortality. In a meta-analysis of 11 cohort studies from 2013, Hoek et al. reported excess risk per $10 \mu g/m^3$ increase in $PM_{2.5}$ of 6% for all-cause and 11% for CVD mortality (Hoek et al., 2013). Still, results on specific causes of death other than CVD are sparse and heterogeneous. While some studies on $PM_{2.5}$ and respiratory disease (RD) mortality detected associations (Carey et al., 2013), the majority did not (Beelen et al., 2008; Cesaroni et al., 2013; Dimakopoulou et al., 2014; Hvidtfeldt et al., 2019; Pope III et al., 2015, 2019; Villeneuve et al., 2015). Furthermore, only a few studies examined the association of long-term exposure to $PM_{2.5}$ with diabetes mortality (Brook et al., 2013; Crouse et al., 2015; Lim et al., 2018; Pope III et al., 2015), suggesting even stronger associations than those observed for all-cause and CVD mortality (Brook et al., 2013; Crouse et al., 2015; Lim et al., 2018).

Road traffic noise is the major environmental stressor which has been recently established as a risk factor for CVD and linked to all-cause and CVD mortality (Halonen et al., 2015; H  ritier et al., 2018; Recio et al., 2017). Road traffic noise shares one of the major sources with air pollution (traffic) and may be an important confounder of an association between air pollution and mortality, yet few studies had data to examine this. Hvidtfeldt et al. reported a substantial confounding by road traffic noise for the association between $PM_{2.5}$ and all-cause mortality with a reduction of hazard ratio (HR) from 1.13 [95% confidence interval (CI): 1.05–1.21] to 1.06 (95% CI: 0.98–1.15) per $5 \mu g/m^3$ (Hvidtfeldt et al., 2019). Similarly, a nationwide Swiss Cohort Study reported confounding of an association between $PM_{2.5}$ and myocardial infarction (MI) mortality by road traffic noise (HRs per $10 \mu g/m^3$ increase with and without noise adjustment: 1.05 (95% CI: 1.01–1.09) and 1.02 (95% CI: 0.97–1.07), respectively) (H  ritier et al., 2018). Based on these findings, H  ritier et al. concluded that air pollution studies not adequately adjusting for traffic noise may overestimate the

CVD burden of air pollution.

Here, we examined the association between long-term exposure to air pollution and total, CVD, RD, and diabetes mortality in a low-exposure Danish cohort, after adjusting for individual lifestyle factors and road traffic noise.

2. Materials and Methods

2.1. Study participants

The Danish Nurse Cohort (Hundrup et al., 2012) was initiated in 1993 when 23,170 female members (> 44 years old) of the Danish Nurse Organization (95% of all nurses in Denmark) were invited to answer a questionnaire about their weight and height, lifestyle (diet, smoking habits, alcohol consumption, physical activity), work-related stress, shift work, self-reported health, and reproductive history, to which 19,898 responded. In 1999, the cohort was expanded by including another 8,833 nurses (newly invited nurses who turned 44 years old in the period 1993–1999, or re-invited non-responders from 1993). The cohort was linked to the Danish Civil Registration System (Pedersen, 2011) to obtain information on residential address history from 1 January 1971 to 31 December 2013 and the vital status during the follow-up until 31 December 2013 (active, date of death, or emigration). We obtained information on geographical coordinates of the nurses' residential addresses from the Danish Address Database.

Of the total 28,731 nurses recruited in the 1993 or 1999, we excluded four nurses who were inactive (died, emigrated, or disappeared) in the Danish Civil Registration System before cohort baseline, 907 with missing exposure data, and 3,279 with missing information on individual risk factors, leaving 24,541 subjects in the final analysis.

2.2. Definition of mortality outcome

We obtained the cause-specific mortality data from the Danish Register of Causes of Death (Helweg-Larsen, 2011), which contains data on underlying and up to three contributory causes of death. Causes of deaths were coded according to the International Classification of Diseases 8th revision [ICD-8; World Health Organization (WHO), 1965] (before 1994) or the 10th revision (ICD-10; WHO, 1992) (since 1994) (ICD-9 coding was never implemented in Denmark). We defined total mortality as all deaths occurring during follow-up, excluding external causes such as injuries and accidents (ICD-10: V01–X59, X85–Y84, ICD-8: 8870), which were censored at the date of death, but including 38 deaths of unknown cause and 75 deaths from suicide (ICD-10: X60–84, ICD-8: 9503, 9508, 9530). In addition, we investigated the following causes of death using the underlying cause of death: CVD (ICD-10: I00–99, ICD-8: 4100, 4129, 4279, 4339, 4369, 4412, 4500), ischemic heart disease (IHD) (ICD-10: I20–25, ICD-8: 4100, 4129), stroke (ICD-10: I60–69, ICD-8: 4339, 4369), other CVD (ICD-10: I00–09, I26–28, I30–50, I70–99, ICD-8: 4279, 4412, 4500), RD (ICD-10: J00–99) and COPD (ICD-10: J41–44). Additionally, we defined the following cause-specific mortality based on underlying or contributing cause of death: diabetes (ICD-10: E10–E14) and hypertension (ICD-10: I10–15, ICD-8: 4010).

2.3. Assessment of air pollution concentration

We used the Danish air pollution dispersion modeling system (DEHM/UBM/AirGIS) to estimate air pollution exposure at the

participants' residence. The validated DEHM/UBM/AirGIS (<http://au.dk/airgis/>) model system (Jensen et al., 2001, 2017; Khan et al., 2019) consists of three air pollution models operating at different spatial scales (DEHM, UBM, OSPM) from the integrated air pollution model system THOR (Brandt et al., 2001c), which incorporates contributions from regional, urban, and local sources, respectively. The Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012; Christensen 1997; Frohn et al., 2002) was applied to obtain the long-range transport contribution of regional pollution components from regional sources. The Urban Background Model (UBM) (Brandt et al., 2003, 2001a, 2001b, 2001c) was used for calculating the contribution of components from local sources to the local background, on a $1 \text{ km} \times 1 \text{ km}$ resolution grid. Finally, the direct contribution of the closest road near the residential address front door was estimated with the Operational Street Pollution Model (OSPM) (Berkowicz, 2000; Ketzel et al., 2012). As input parameters for the OSPM, a semi-automatic system (AirGIS) has been constructed using Geographic Information System (GIS) and available Danish registers (Hertel et al., 2013). The DEHM/UBM/AirGIS system is considered state-of-the-art in the field of exposure assessment, and the OSPM applied for the street pollution component is

used in > 20 countries worldwide (Hvidtfeldt et al., 2018; Kakosimos et al., 2010; Ketzel et al., 2012).

The required emission input data for local scale exposure modeling has been established for $\text{PM}_{2.5}$ and particulate matter with a diameter of $< 10 \mu\text{m}$ (PM_{10}) from 1990 for Denmark. Therefore, for each residential address, we assigned annual mean concentrations of $\text{PM}_{2.5}$, PM_{10} and nitrogen dioxide (NO_2) from 1990 to the corresponding year of follow-up, to calculate 3-year running means of $\text{PM}_{2.5}$, PM_{10} , and NO_2 . The mean of three consecutive years of the annual concentrations of $\text{PM}_{2.5}$, PM_{10} , and NO_2 was the main exposure proxy, as this was the longest possible exposure window between 1990, when modeling of $\text{PM}_{2.5}$ began, and 1-year before 1993, when the study follow-up began (we applied a 1-year lag since the study started on 1 April 1993).

2.4. Assessment of residential road traffic noise

Exposure to residential road traffic noise was calculated by the use of the Nord2000 method, a state-of-the-art traffic noise propagation model for estimating noise contribution from road traffic and wind turbines (DELTA, 2001). This method utilizes the following input

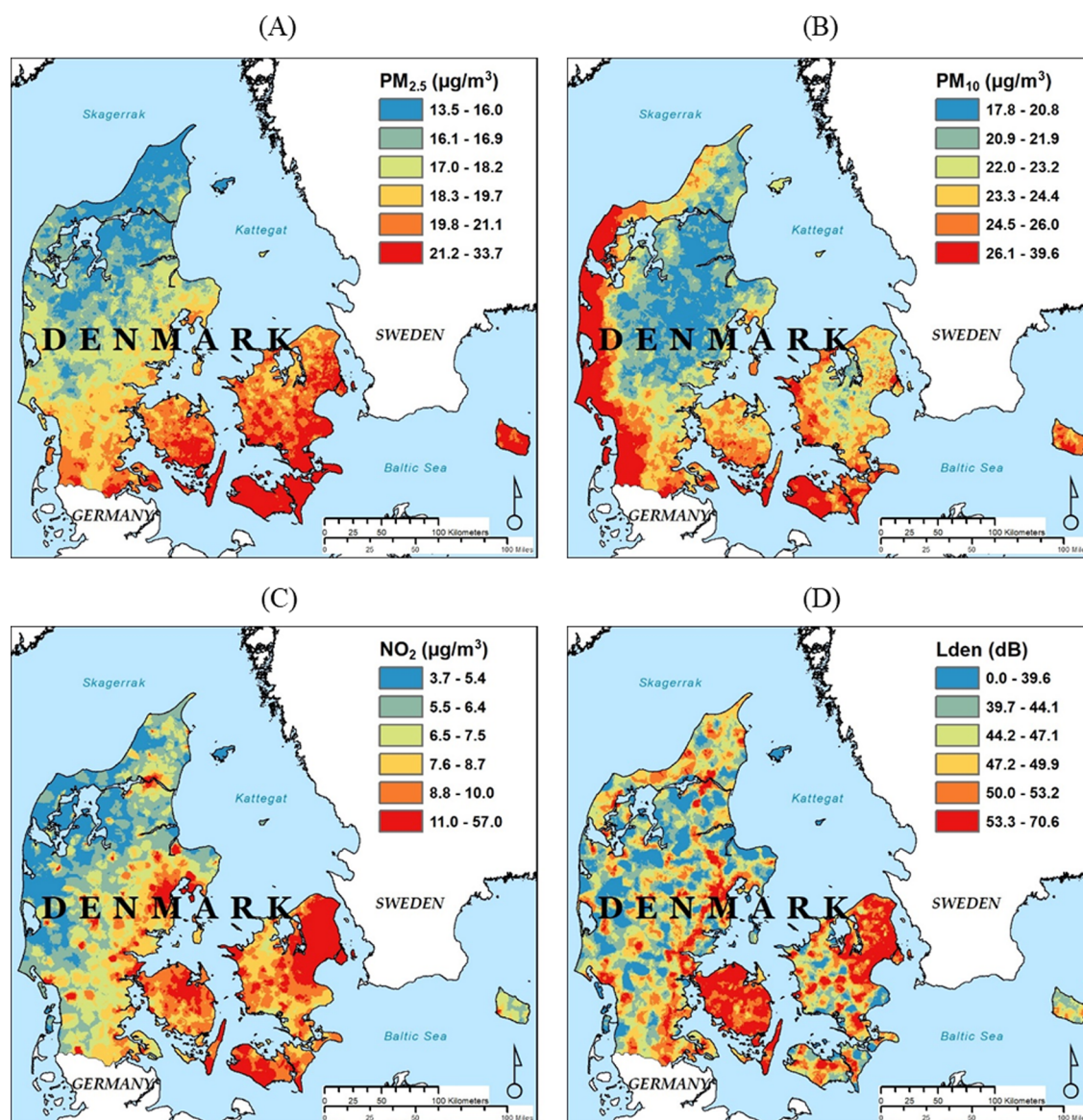


Fig. 1. Annual mean residential exposure levels (smoothed) for $\text{PM}_{2.5}$ (A), PM_{10} (B), NO_2 (C), and L_{den} (D) in the Danish Nurse Cohort at year of cohort entry (1993 or 1999).

variables: geocodes of the address, the height of residence above street level, annual average daily traffic, traffic characteristics (composition, speed, road type), building polygons for surrounding buildings, and meteorology (temperature, cloud coverage, and wind speed and direction). For the participants' residential addresses between the years of 1990 and 2013, the yearly average road traffic noise levels were calculated to estimate noise contribution from roads within a 3 km radius from the address. The annual road traffic noise levels were estimated as the equivalent continuous A-weighted sound pressure level at the most exposed residential façade for the day, evening, and night, and expressed as L_{den} (the annual weighted noise levels of 24-hour average throughout the day, evening and night with 5 dB penalty for the evening and 10 dB penalty in the night estimated noise level). Since we had an accurate date of moving residential address, we calculated the annual mean of L_{den} at the year of an address change as the mean of the L_{den} levels at two addresses (old and the new). The Nord2000 returned the noise levels for addresses in a remote area with less traffic noise

contributions as 0 dB, even though it never occurs in reality due to noise contribution from sources other than traffic, e.g., vegetation. In this study, we used the mean of three consecutive years of L_{den} with 1-year lag as a confounding variable.

2.5. Statistical analysis

We used a time-varying Cox proportional hazards regression model with age as the underlying time scale to investigate total and cause-specific mortality as a function of air pollution exposure. The follow-up period began on the date participants responded to the questionnaire (1 April 1993 or 1 April 1999), and the end of the follow-up period was the date of death (event), emigration, or 31 December 2013, whichever came first.

We modeled the association in crude models (Model 1) only adjusting for age (underlying time scale). In fully adjusted models (Model 2), we further adjusted for potential individual risk factors collected at

Table 1

Descriptive statistics for 24,541 female nurses from the Danish Nurse Cohort at the cohort baseline in 1993 or 1999 by the status (Alive/Dead) at the end of follow-up.

Characteristics	Total N = 24,541	Alive N = 20,833	Dead ^a N = 3,708	P-value ^b
Age at study start (years), mean \pm SD	53.2 \pm 8.0	51.6 \pm 6.5	62.1 \pm 9.9	< 0.0001
Body mass index (kg/m ²), mean \pm SD	23.7 \pm 3.5	23.7 \pm 3.5	23.6 \pm 3.8	0.0092
Body mass index, n (%)				< 0.0001
Underweight (< 18.5 kg/m ²)	611 (2.5)	407 (2.0)	204 (5.5)	
Normal weight (18.5–24.9 kg/m ²)	16,933 (69.0)	14,518 (69.7)	2,415 (65.1)	
Overweight (25–29.9 kg/m ²)	5,605 (22.8)	4,757 (22.8)	848 (22.9)	
Obese (\geq 30 kg/m ²)	1,392 (5.7)	1,151 (5.5)	241 (6.5)	
Smoking status, n (%)				< 0.0001
Never	8,438 (34.4)	7,622 (36.6)	816 (22.0)	
Previous	7,571 (30.9)	6,468 (31.0)	1,103 (29.7)	
Current	8,532 (34.8)	6,743 (32.4)	1,789 (48.2)	
Alcohol consumption, n (%)				< 0.0001
None (0 drinks/week)	3,772 (15.4)	2,854 (13.7)	918 (24.8)	
Moderate (1–14 drinks/week)	15,153 (61.7)	13,199 (63.4)	1,954 (52.7)	
Heavy (\geq 15 drinks/week)	5,616 (22.9)	4,780 (22.9)	836 (22.5)	
Physical activity, n (%)				< 0.0001
Low	1,631 (6.6)	1,120 (5.4)	511 (13.8)	
Medium	16,355 (66.6)	13,857 (66.5)	2,498 (67.4)	
High	6,555 (26.7)	5,856 (28.1)	699 (18.9)	
Avoid fatty meat, n (%)	22,180 (90.4)	19,022 (91.3)	3,158 (85.2)	< 0.0001
Working status, n (%)	19,267 (78.5)	17,721 (85.1)	1,546 (41.7)	< 0.0001
Marital status, n (%)				< 0.0001
Married	17,305 (70.5)	15,419 (74.0)	1,886 (50.9)	
Separated/divorced	3,180 (13)	2,670 (12.8)	510 (13.8)	
Single	2,429 (9.9)	1,713 (8.2)	716 (19.3)	
Widow	1,627 (6.6)	1,031 (4.9)	596 (16.1)	
Use of hormone therapy, n (%)				< 0.0001
Never-users	17,788 (72.5)	15,430 (74.1)	2,358 (63.6)	
Past-users	2,477 (10.1)	1,823 (8.8)	654 (17.6)	
Current-users	4,276 (17.4)	3,580 (17.2)	696 (18.8)	
Has hypertension ^c , n (%)	3,152 (12.9)	2,324 (11.2)	828 (22.4)	< 0.0001
Has diabetes ^d , n (%)	288 (1.2)	195 (0.9)	93 (2.5)	< 0.0001
Had MI ^e , n (%)	183 (0.7)	78 (0.4)	105 (2.9)	< 0.0001
Degree of urbanicity ^f , n (%)				< 0.0001
Rural	9,763 (40.6)	8,333 (40.8)	1,430 (39.6)	
Suburban	10,581 (44.0)	9,050 (44.3)	1,531 (42.4)	
Urban	3,681 (15.3)	3,033 (14.9)	648 (18.0)	
Three-year running mean at baseline with 1 year lag				
PM _{2.5} , mean \pm SD (μ g/m ³)	20.5 \pm 3.9	20.3 \pm 3.8	21.4 \pm 4.1	< 0.0001
PM ₁₀ , mean \pm SD (μ g/m ³)	24.4 \pm 4.2	24.3 \pm 4.1	25.5 \pm 4.5	< 0.0001
NO ₂ , mean \pm SD (μ g/m ³)	13.4 \pm 8.0	13.2 \pm 7.9	14.1 \pm 9.0	< 0.0001
L_{den} , mean \pm SD (dB)	52.8 \pm 8.0	52.7 \pm 8.0	53.7 \pm 8.0	< 0.0001

Abbreviations: SD-Standard deviation; PM_{2.5}-Particulate matter aerodynamic diameter < 2.5 μ m; PM₁₀-Particulate matter aerodynamic diameter < 10 μ m; NO₂-Nitrogen dioxide; L_{den} -The annual weighted noise levels of 24-hour average; MI-Myocardial infarction.

^a Total mortality (see Methods for details).

^b *t*-test for continuous variables and chi-square test for discrete variables.

^c n = 24,512.

^d n = 24,362.

^e n = 24,422.

^f n = 24,025.

baseline: body mass index (BMI) ($< 18.5 \text{ kg/m}^2$, $18.5\text{--}24.9 \text{ kg/m}^2$, $25\text{--}29.9 \text{ kg/m}^2$, or $\geq 30 \text{ kg/m}^2$), smoking status (never, previous, or current), alcohol consumption [none (0 drinks per week), moderate (1–15 drinks per week), or heavy (> 15 drinks per week)], leisure-time physical activity (low, medium, or high), avoidance of fatty meat (no or yes), working at the time of questionnaire (no or yes), marital status (married, separated/divorced, single, or widow), and use of hormone therapy (never, past, or current). Additionally, in a third model (Model 3), we adjusted for road traffic noise.

Pollutants were first considered separately using single-pollutant models and then simultaneously using two-pollutant models to examine the effect of each pollutant on mortality independently of the effect of other pollutants. We did not model $\text{PM}_{2.5}$ and PM_{10} together since they were highly correlated (Pearson's correlation coefficient > 0.7 ; Table S1 in [Supplementary Material](#)).

We evaluated the assumption of linearity of the association between air pollution and the risk of mortality by examining the graphical presentation of a functional form of an association between air pollutants and mortality with restricted cubic spline in the “rms” package in R with 3 degrees of freedom.

Estimates were expressed as HR with 95% CI, per interquartile range (IQR) increase in each pollutant levels to facilitate direct comparison between pollutants, and also per $5 \mu\text{g/m}^3$ increase in each pollutant levels.

To examine the effects of air pollution at low levels, we performed additional analyses by including only person-years with exposure below pre-specified thresholds (e.g., $25 \mu\text{g/m}^3$, $20 \mu\text{g/m}^3$, and $15 \mu\text{g/m}^3$ for $\text{PM}_{2.5}$; $30 \mu\text{g/m}^3$ and $20 \mu\text{g/m}^3$ for PM_{10} ; $30 \mu\text{g/m}^3$, $20 \mu\text{g/m}^3$, and $15 \mu\text{g/m}^3$ for NO_2).

Finally, we examined potential effect modifications of the association between air pollutants and total mortality by including an interaction term between the modifier and the exposure in the model and using the likelihood ratio test. These included age, physical activity, BMI, smoking status, myocardial infarction (MI), hypertension, diabetes, degree of urbanicity, average income of municipality (low, medium, and high; defined by average income level in the municipality of the residence at cohort baseline), regional background $\text{PM}_{2.5}$ levels

(low, medium, and high; ascertained using tertiles of mean $\text{PM}_{2.5}$ levels at the cohort baseline in 98 Danish municipalities), and regions defined by the five administrative areas of Denmark (Capital Region of Denmark, Central Denmark Region, North Denmark Region, Region of Southern Denmark, Region Zealand). We examined the effect modification by region to explore whether the association between $\text{PM}_{2.5}$ and mortality is stronger in the southeastern regions of Denmark, where $\text{PM}_{2.5}$ is higher due to high levels of long-range transported particles from central and eastern Europe ([Fig. 1](#)).

Analyses and graphical presentations of data were performed using R software, version 3.6.1 (R Project for Statistical Computing) and ArcGIS 10.7.1 (ESRI, Redlands, CA). All statistical tests were two-sided, and $p\text{-value} < 0.05$ was considered statistically significant.

3. Results

3.1. Description of the study population and exposure

With a total of 24,541 participants, the mean follow-up time was 17.4 years, giving a total of 428,142 person-years, during which we observed 3,708 deaths (15.1% of all participants). There were 843 (22.7%) deaths from CVD, 292 (7.9%) from IHD, 269 (7.3%) from stroke, 104 (2.8%) from hypertension, 241 (6.5%) from other CVD, 310 (8.3%) from RD, 172 (4.6%) from COPD, and 64 (1.7%) from diabetes.

Comparing the baseline characteristics ([Table 1](#)), participants who died during follow-up were older, had higher BMI, were more likely to be current smokers, non-drinkers, physically inactive, consume fatty meat, not married (or widowed), and more likely to have hypertension, diabetes, or MI, as compared to those who remained alive at the end of follow-up. Participants who died were also exposed to higher levels of all pollution and road traffic noise at cohort baseline residence than those who remained alive at the end of follow-up. [Table S6](#) in [Supplementary Material](#) presents descriptive statistics for included and excluded participants. Nurses who were excluded from the study ($n = 4,186$) were older than nurses who were included ($n = 24,541$). They were more likely to have been current smokers, none alcohol consumers, less physically active, and consumers of fatty meat. These

Table 2

Association between air pollution (3 year-running mean with 1-year lag, scaled per interquartile range) and total and cause-specific mortality in the Danish Nurse Cohort.

Air pollutant	Interquartile range ($\mu\text{g/m}^3$)	Model 1 ^a	Model 2 ^b	Model 3 ^c	Two pollutant ^d		
		HR (95% CI)	HR (95% CI)	Model2 + Noise HR (95% CI)	Model2 + NO_2 HR (95% CI)	Model2 + $\text{PM}_{2.5}$ HR (95% CI)	Model2 + PM_{10} HR (95% CI)
Total							
$\text{PM}_{2.5}$	4.39	1.18 (1.14, 1.23)	1.06 (1.01, 1.10)	1.06 (1.01, 1.11)	1.12 (1.06, 1.18)	–	–
PM_{10}	5.20	1.19 (1.14, 1.24)	1.06 (1.01, 1.11)	1.06 (1.01, 1.11)	1.11 (1.05, 1.17)	–	–
NO_2	7.34	1.04 (1.00, 1.07)	0.98 (0.95, 1.01)	0.96 (0.92, 1.00)	–	0.93 (0.90, 0.97)	0.95 (0.91, 0.98)
Cardiovascular disease							
$\text{PM}_{2.5}$	4.39	1.31 (1.21, 1.43)	1.12 (1.03, 1.23)	1.14 (1.03, 1.26)	1.24 (1.10, 1.39)	–	–
PM_{10}	5.20	1.33 (1.22, 1.45)	1.14 (1.04, 1.25)	1.15 (1.04, 1.27)	1.23 (1.10, 1.38)	–	–
NO_2	7.34	1.04 (0.97, 1.10)	0.98 (0.92, 1.04)	0.97 (0.89, 1.05)	–	0.90 (0.83, 0.97)	0.91 (0.85, 0.98)
Respiratory disease							
$\text{PM}_{2.5}$	4.39	1.22 (1.05, 1.41)	1.01 (0.86, 1.18)	0.98 (0.83, 1.16)	1.02 (0.84, 1.25)	–	–
PM_{10}	5.20	1.17 (1.00, 1.35)	0.96 (0.81, 1.14)	0.94 (0.80, 1.12)	0.96 (0.79, 1.17)	–	–
NO_2	7.35	1.07 (0.96, 1.18)	0.99 (0.89, 1.10)	0.94 (0.82, 1.08)	–	0.98 (0.86, 1.12)	1.00 (0.88, 1.14)
Diabetes							
$\text{PM}_{2.5}$	4.39	1.88 (1.47, 2.41)	1.47 (1.11, 1.95)	1.41 (1.05, 1.90)	1.52 (1.06, 2.19)	–	–
PM_{10}	5.20	1.86 (1.45, 2.37)	1.45 (1.08, 1.93)	1.38 (1.03, 1.86)	1.44 (1.01, 2.04)	–	–
NO_2	7.34	1.26 (1.05, 1.51)	1.15 (0.95, 1.40)	1.07 (0.83, 1.37)	–	0.97 (0.75, 1.24)	1.01 (0.8, 1.26)

Abbreviations: HR-Hazard ratio; CI-Confidence interval; $\text{PM}_{2.5}$ -Particulate matter aerodynamic diameter $< 2.5 \mu\text{m}$; PM_{10} -Particulate matter aerodynamic diameter $< 10 \mu\text{m}$; NO_2 -Nitrogen dioxide.

^a Crude model, adjusting for age (underlying time scale).

^b Fully adjusted model, adjusted for age (underlying time scale), body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy.

^c Model 3: Model2 adjusted additionally for 3-year running mean for L_{den} .

^d Two-pollutant models.

excluded cohort participants were also more likely than included participants to be non-working status, not married (or widowed), ever-users of hormone therapy, and more likely to have hypertension, diabetes, or MI. Furthermore, the excluded subjects were more likely to live in rural places and be exposed to higher levels of PM.

Mean levels of $PM_{2.5}$, PM_{10} , and NO_2 at the year of the cohort baseline (1993 or 1999) were 20.5, 24.4, and 13.4 $\mu g/m^3$, respectively, and mean levels of L_{den} were 52.8 dB (Table 1), showing large geographical variations (Fig. 1). While levels of NO_2 and L_{den} are highest around urban areas, where population and traffic density are highest, $PM_{2.5}$ levels in Denmark are also high in the South-Eastern part of the country (Fig. 1).

The correlation coefficients between the different pollutants and L_{den} were in the range of 0.20–0.60 (Table S1 in the Supplementary Material).

3.2. Association between mortality and air pollution exposure

We found positive associations of all pollutants and total, CVD, RD,

and diabetes mortality in Model 1, which attenuated after adjustment for individual-level confounders in Model 2 (Table 2). In Model 2, we found the association between a three-year mean of $PM_{2.5}$ and total mortality with an HR of 1.06 (95% CI: 1.01–1.10) per IQR of 4.39 $\mu g/m^3$ increase. The corresponding HRs for CVD and diabetes mortality were 1.12 (95% CI: 1.03–1.23) and 1.47 (95% CI: 1.11–1.95), respectively, while there was no association with RD mortality. The effect sizes in Model 2 for PM_{10} were similar to those for $PM_{2.5}$, while no statistically significant associations were detected with NO_2 . HRs remained unchanged after adjustment for L_{den} for total mortality, slightly increased for CVD mortality, and slightly decreased for diabetes mortality (Model 3, Table 2).

In the two-pollutant models, the adjustment for NO_2 resulted in enhanced HRs for $PM_{2.5}$, while HRs for NO_2 attenuated after adjusting for $PM_{2.5}$ and PM_{10} , except for the HRs of NO_2 for RD mortality where all associations were null (Table 2).

We identified a linear association between $PM_{2.5}$ with diabetes mortality, supra-linear associations with total and CVD mortality (steeper curve at low exposure), and a slightly inverted U-shape

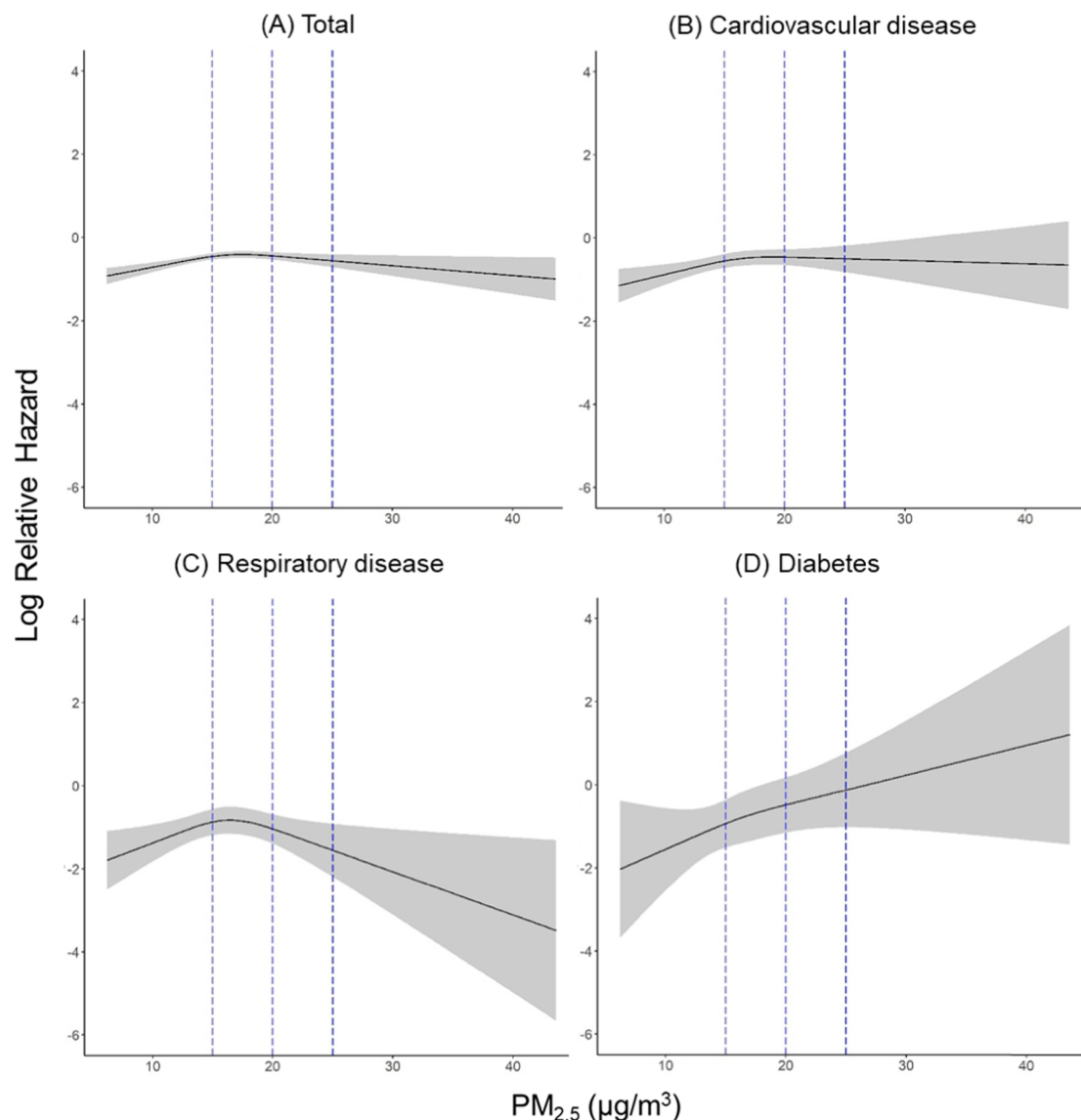


Fig. 2. Restricted spline curves for the association^a between $PM_{2.5}$ (3 year-running mean with 1-year lag) and (A) total, (B) cardiovascular disease, (C) respiratory diseases, and (D) diabetes mortality (blue lines represent thresholds at 15, 20 and 25 $\mu g/m^3$). ^a Fully adjusted model, adjusted for age (underlying time scale), body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy.

exposure–response curve for the association with RD mortality, which was linear between 5th and 95th percentiles of exposure range (Fig. 2; exposure–response curves for PM₁₀ and NO₂: see Figs. S1 and S2 in supplementary material).

We observed stronger associations in a subset of person-years with PM_{2.5} < 20 µg/m³, with HRs of 1.18 (95% CI: 1.10–1.26) for total, 1.24 (95% CI: 1.08–1.43) for CVD, 1.29 (95% CI: 1.03–1.62) for RD, and 1.55 (95% CI: 0.91–2.65) for diabetes mortality (Table 3; Threshold analyses for PM₁₀ and NO₂: see Tables S2 and S3 in the supplementary material, respectively).

The analyses with subtypes of CVD show the strongest associations of PM_{2.5} with hypertension with an HR of 1.23 (95% CI: 0.96–1.57) and IHD with an HR of 1.18 (95% CI: 1.01–1.37), followed by weaker associations with other CVD and stroke (Fig. 3; Numerical results in Table S4 in Supplementary Material). We found no association of NO₂ with any subtypes of CVD, and no associations between any pollutants with COPD mortality.

We detected a statistically significant effect modification by urbanicity on the association of PM_{2.5} and total mortality, suggesting that nurses living in rural or suburban areas had stronger association with PM_{2.5} than those living in urban areas (Fig. 4, Table S5 in Supplementary Material). In line with this finding and supra-linear exposure–response curves for PM_{2.5} (Fig. 2), we found a stronger association in regions with low-levels of PM_{2.5} (< 15.47 µg/m³). The associations with PM_{2.5} were stronger in those who were younger than 60 years, were less physically active, or had diabetes or history of MI, although the interaction terms did not reach statistical significance.

4. Discussion

In a large nationwide cohort of female nurses in Denmark, we detected significant positive associations between long-term exposures to PM_{2.5} and total, CVD, and diabetes mortality, which were independent from road traffic noise. Associations persisted and were even stronger at the PM_{2.5} levels below the current EU limit values of 25 µg/m³ and WHO recommendation of 10 µg/m³, where associations with RD also were observed. The associations were strongest for diabetes,

hypertension, and IHD mortality.

Our fully adjusted HR for an association between PM_{2.5} and total mortality is comparable with, or slightly higher than, those reported in other studies in European and North American settings (see Fig. S3 in supplementary material) (Beelen et al., 2008, 2014a; Carey et al., 2013; Cesaroni et al., 2013; Crouse et al., 2012; Lepeule et al., 2012; Pappin et al., 2019; Pope III et al., 2019; Villeneuve et al., 2015). Our associations are notably weaker than those reported in the recent Danish Diet, Cancer and Health (DCH) study, including men and women from two largest cities in Denmark [HR: 1.13 (95% CI: 1.05–1.21) per 5 µg/m³ increment in PM_{2.5}] (Hvidtfeldt et al., 2019). However, Hvidtfeldt et al. detected significant effect modification by gender, and their finding of the weak associations in women, with HR of 1.05 (95% CI: 0.97–1.14) agrees remarkably well with our effect estimate of 1.06 (95% CI: 1.01–1.12) per 5 µg/m³ increment in PM_{2.5} in female Danish nurses. A few other studies suggested weaker associations of PM_{2.5} with mortality in women than men (Cesaroni et al., 2013; Pappin et al., 2019; Wong et al., 2015) or found associations only in men (Beelen et al., 2014a; Di et al., 2017), while some other studies found no differences in susceptibility to air pollution by gender (Brook et al., 2013; Pope III et al., 2002). Therefore, further nationwide investigations are needed to examine the gender difference in effect of air pollution in Denmark.

Here we present novel findings that associations between PM_{2.5} and total, CVD, and diabetes mortality were not confounded by road traffic noise. This is in contrast to the Danish DCH study, where the adjustment for road traffic noise resulted in a significant attenuation of the association between PM_{2.5} and all-cause mortality from an HR of 1.13 (95% CI: 1.05–1.21) to 1.06 (95% CI: 0.98–1.15), but did not affect the association with CVD mortality (Hvidtfeldt et al., 2019). The differences could be explained by the DCH cohort being a highly urban cohort, consisting of the population from the two largest Danish cities, where road traffic noise has a stronger correlation with PM_{2.5} and possibly stronger association with mortality than in our cohort of nurses living mainly in rural and provincial areas. A nationwide Swiss Cohort Study also reported substantial confounding of an association between PM₂ and MI mortality by road traffic noise, where HRs per 10 µg/m³

Table 3

Association between total and cause-specific mortality and exposure to PM_{2.5} (3 year-running mean with 1-year lag), below various threshold values.

	Mortality cases, n	Subject at risk, n	Model 1 ^a HR (95% CI)	Model 2 ^b HR (95% CI)	Model 3 ^c Model 2 + Noise HR (95% CI)
Total					
No threshold	3,708	24,541	1.18 (1.14, 1.23)	1.06 (1.01, 1.10)	1.06 (1.01, 1.11)
< 25 µg/m ³	3,671	24,500	1.22 (1.16, 1.27)	1.08 (1.03, 1.14)	1.08 (1.03, 1.14)
< 20 µg/m ³	3,317	24,080	1.33 (1.24, 1.41)	1.18 (1.10, 1.26)	1.19 (1.11, 1.27)
< 15 µg/m ³	1,681	21,466	1.35 (1.16, 1.58)	1.26 (1.08, 1.47)	1.27 (1.08, 1.49)
Cardiovascular disease					
No threshold	843	24,541	1.31 (1.21, 1.43)	1.12 (1.03, 1.23)	1.14 (1.03, 1.26)
< 25 µg/m ³	835	24,500	1.38 (1.26, 1.52)	1.18 (1.06, 1.30)	1.19 (1.07, 1.32)
< 20 µg/m ³	752	24,080	1.46 (1.27, 1.67)	1.24 (1.08, 1.43)	1.27 (1.01, 1.46)
< 15 µg/m ³	369	21,466	1.20 (0.87, 1.66)	1.13 (0.82, 1.56)	1.14 (0.82, 1.58)
Respiratory disease					
No threshold	310	24,541	1.22 (1.05, 1.41)	1.01 (0.86, 1.18)	0.98 (0.83, 1.16)
< 25 µg/m ³	308	24,500	1.27 (1.08, 1.49)	1.03 (0.87, 1.23)	1.01 (0.84, 1.21)
< 20 µg/m ³	288	24,080	1.58 (1.27, 1.96)	1.29 (1.03, 1.62)	1.27 (1.00, 1.60)
< 15 µg/m ³	136	21,466	1.56 (0.91, 2.69)	1.40 (0.81, 2.41)	1.38 (0.79, 2.40)
Diabetes					
No threshold	64	24,541	1.88 (1.47, 2.41)	1.47 (1.11, 1.95)	1.41 (1.05, 1.90)
< 25 µg/m ³	60	24,500	1.82 (1.31, 2.53)	1.34 (0.95, 1.90)	1.27 (0.89, 1.82)
< 20 µg/m ³	50	24,080	2.27 (1.33, 3.87)	1.55 (0.91, 2.65)	1.44 (0.83, 2.48)
< 15 µg/m ³	19	21,466	1.63 (0.37, 7.22)	1.34 (0.31, 5.89)	1.26 (0.29, 5.54)

Abbreviations: HR-Hazard ratio; CI-Confidence interval. Unit for HR: 4.39 µg/m³.

^a Crude model, adjusting for age (underlying time scale).

^b Fully adjusted model, adjusted for age (underlying time scale), body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy.

^c Model 3: Model2 adjusted additionally for 3-year running mean for I_{den}.

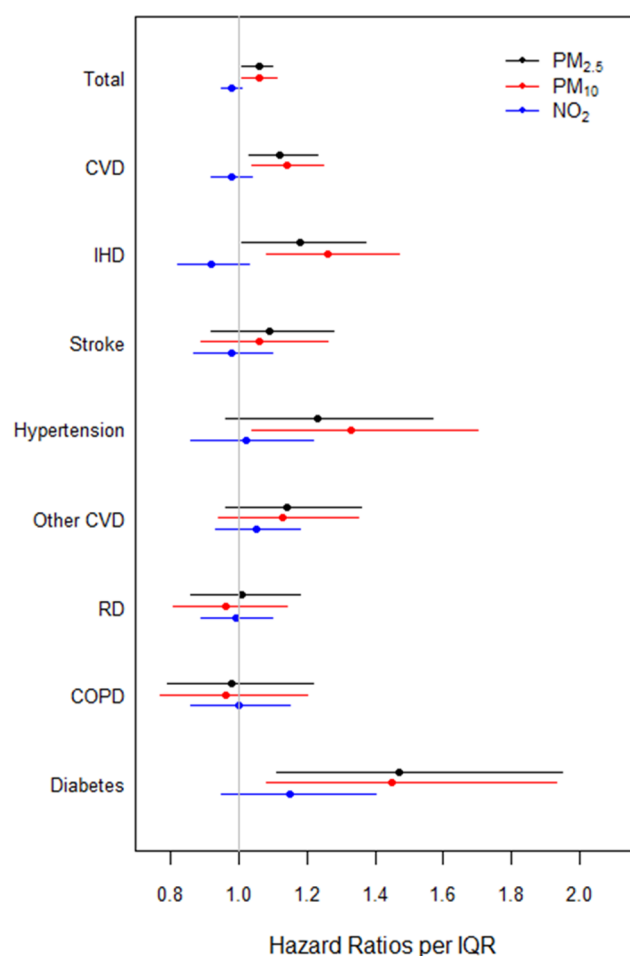


Fig. 3. Hazard ratio (HR) estimates^a and confidence interval (CI) for total mortality and eight causes of death associated with interquartile range (IQR) increase in each air pollutant levels. Abbreviations: CVD-Cardiovascular disease; IHD-Ischemic heart disease; RD-Respiratory disease; COPD-Chronic obstructive pulmonary disease. ^aFrom the fully adjusted models (Model 2), adjusted for age (underlying time scale), body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy. The numerical results in Table S4 in the Supplementary Material.

increase with and without noise adjustment were 1.05 (95% CI: 1.01–1.09) vs. 1.02 (95% CI: 0.97–1.07) for PM_{2.5} (H  ritier et al., 2018). With rapidly increasing evidence on the health effects related to exposure to road traffic noise (World Health Organization, 2018) including studies on mortality (Halonen et al., 2015; H  ritier et al., 2018; Recio et al., 2017), more studies will need to explore whether road traffic noise confounds the association of air pollution with mortality.

We observed more pronounced HRs in a subset of person-years with PM_{2.5} levels below 25 $\mu\text{g}/\text{m}^3$ (EU limit value) for total mortality, and below 20 $\mu\text{g}/\text{m}^3$ for total, CVD, and RD mortality (Table 3), suggesting no lower threshold below which air pollution is safe and even steeper exposure–response function in the lowest exposure range, as illustrated in Fig. 2. This is in line with results from Di et al. who reported stronger associations [HR: 1.136 (95% CI: 1.131–1.141) per 10 $\mu\text{g}/\text{m}^3$] with mortality below USA National Ambient Air Quality Standard of 12 $\mu\text{g}/\text{m}^3$ in large US Medicare study (Di et al., 2017), as well as with recent review which concluded that there is strong agreement across existing studies that air pollution health effects are still observable at low concentrations (Papadogeorgou et al., 2019). Our results support the idea that adverse effects of air pollution exist even below current EU limit values and likely even below WHO recommendations, and the current US standard (Beelen et al., 2014a; Di et al., 2017; Papadogeorgou et al.,

2019). Our results add to a large body of evidence on adverse effects of air pollution at the levels below current limit values, which make strong support to governments to commit to clean air legislation in order to reduce air pollution related health burden. Our findings directly suggest that the current air quality standards need to be re-evaluated, and that further improvements in air quality would benefit public health (Di et al., 2017; Papadogeorgou et al., 2019).

In agreement with our findings and meta-analyses from 2013 (Hoek et al., 2013), most (Cesaroni et al., 2013; Crouse et al., 2012, 2015; Hvidtfeldt et al., 2019; Lepeule et al., 2012; Pope III et al., 2015; Villeneuve et al., 2015), but not all (Beelen et al., 2008, 2014b; Carey et al., 2013) studies, found the association of PM_{2.5} with CVD mortality to be stronger than that with all-cause mortality. Fewer studies have examined cerebrovascular disease or stroke mortality, where we report positive but statistically non-significant associations, in line with the analysis of 22 European cohorts in the ESCAPE study (Beelen et al., 2014b) and the Canadian National Breast Screening Study (Villeneuve et al., 2015). In contrast, no association with stroke mortality was found in the Canadian national-level cohort study (Crouse et al., 2012) or in the Canadian Census Health and Environment Cohort (CanCHEC) (Crouse et al., 2015). Our findings of the strong association between PM_{2.5} and hypertension mortality, stronger than those with total CVD or other CVD-related causes, agree remarkably well with the two other studies on hypertension mortality, a study in the American Cancer Society Cancer Prevention Study II (ACS CPS-II) (Pope III et al., 2015), and a large study of US Veterans (Bowe et al., 2019). Similarly, we detected stronger associations of PM_{2.5} with IHD than with stroke or total CVD mortality, which is in line with the national-level Canadian study (Crouse et al., 2012), CanCHEC analyses (Crouse et al., 2015), ACS CPS-II (Pope III et al., 2015), and the National Institutes of Health-AARP Diet and Health Study (Hayes et al., 2020), while the ESCAPE analyses found no association with IHD, MI, or CVD mortality, but detected a weak positive association with stroke mortality (Beelen et al., 2014b). In summary, our results suggest that the air pollution-contributed CVD mortality burden is mainly driven by IHD- and hypertension-related CVD, which generally agrees well with current evidence.

Our findings of the strong association between PM_{2.5} and diabetes mortality [HR: 2.42 (95% CI: 1.27–4.60) per 10 $\mu\text{g}/\text{m}^3$] are much higher than the results from the other three studies on the topic, all of which also report strong positive and significant associations. The large nationwide Canadian study reported an HR of 1.49 (95% CI: 1.37–1.62) (Brook et al., 2013), and the study based on the ACS CPS-II study found an HR of 1.13 (95% CI: 1.02–1.26) (Pope III et al., 2015) per 10 $\mu\text{g}/\text{m}^3$, while the US NIH-AARP Diet and Health Study found an HR of 1.19 (95% CI: 1.03–1.39) per 10 $\mu\text{g}/\text{m}^3$ (Lim et al., 2018). Although only a few studies examined diabetes mortality as an outcome, they are in line with a large body of evidence on PM_{2.5} and diabetes incidence and a recent GBD study which concluded that associations between PM_{2.5} and type 2 diabetes are larger than those seen with CVD or RD (Bowe et al., 2018). Furthermore, in line with our results (Fig. 2), Brook et al. (Brook et al., 2013) found a linear exposure–response relationship between PM_{2.5} and diabetes mortality, even at low levels (< 10 $\mu\text{g}/\text{m}^3$) and without an apparent lower threshold.

We present novel results for RD mortality, suggesting a supra-linear association, with a steeper linear exposure–response function at the lower end of the exposure range (Fig. 2), with a strong positive and significant association at PM_{2.5} levels < 20 $\mu\text{g}/\text{m}^3$. This finding agrees with the finding of the UK nationwide study [HR: 1.09 (95% CI: 1.05–1.13) per IQR of 1.9 $\mu\text{g}/\text{m}^3$] (Carey et al., 2013), where 75% of the population lived in areas below 20 $\mu\text{g}/\text{m}^3$, which is comparable to our study. However, our results disagree with the majority of the literature that does not detect associations between PM_{2.5} and RD mortality when assuming a linear relationship (Beelen et al., 2008; Cesaroni et al., 2013; Crouse et al., 2015; Dimakopoulou et al., 2014; Hvidtfeldt et al., 2019; Pope III et al., 2015, 2019; Villeneuve et al., 2015), calling

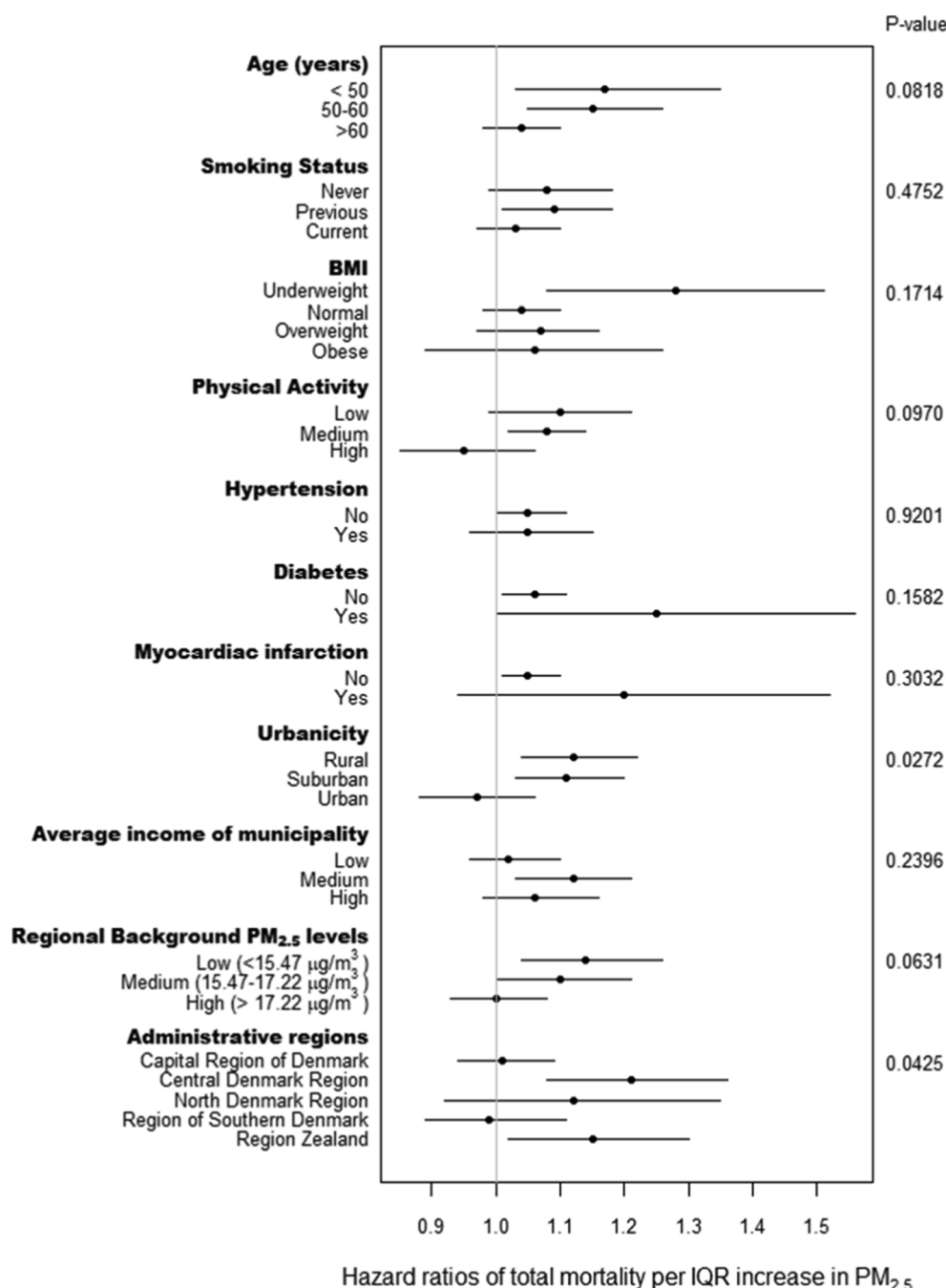


Fig. 4. Modification of the association^a between concentration of PM_{2.5} (3-year running mean with 1-year lag, per interquartile range 4.39 µg/m³) and total mortality (N = 3,708) by baseline characteristics and comorbid conditions among 24,541 participants in the Danish Nurse Cohort. Abbreviations: BMI-Body mass index; IQR-Interquartile range (4.39 µg/m³). ^aFrom the fully adjusted models (Model 2), adjusted for age (underlying time scale), body mass index, smoking status, alcohol consumption, physical activity, fatty meat consumption, working status, marital status, use of hormone therapy; The numerical results in Table S5 in the Supplementary Material.

for more studies to carefully consider the shape of this association at the lower ranges of exposure.

Our lack of association between long-term exposure to NO₂ and mortality is in line with the ESCAPE study on 22 European cohorts (Beelen et al., 2014a) but in disagreement with the majority of studies on NO₂ and total mortality (Beelen et al., 2008; Carey et al., 2013; Cesaroni et al., 2013; Heinrich et al., 2013; Hvidtfeldt et al., 2019; Nieuwenhuijsen et al., 2018; Raaschou-Nielsen et al., 2012). The association between NO₂ and mortality in Denmark has been investigated previously in the DCH cohort (Hvidtfeldt et al., 2019; Raaschou-Nielsen et al., 2012), which detected associations of NO₂ with all-cause [HR: 1.07 (95% CI: 1.04–1.10) per 10 µg/m³] and CVD [HR: 1.11 (95% CI: 1.04–1.17)] mortality (Hvidtfeldt et al., 2019), in the urban cohort. We did, however, find enhanced associations with RD and diabetes mortality when limiting a subset of person-years with NO₂ < 20 and < 15 µg/m³ (Table S3), which reached significance with RD mortality at

NO₂ levels < 15 µg/m³ (1.41; 1.02–1.94 per 7.34 µg/m³).

Our finding of the statistically significant interaction between urbanicity and PM_{2.5}, showing that associations with PM_{2.5} were limited to rural and provincial areas (Fig. 4), is in line with our findings of stronger associations at the lowest PM_{2.5} levels, below 20 and 15 µg/m³. Another explanation for this finding of no association in urban areas is possible relevance of non-traffic PM_{2.5} sources for mortality, such as biomass or long-range transported secondary particles, which dominate suburban and rural areas. However, we did not find clear pattern of association between PM_{2.5} and mortality by region (Fig. 4), where we could have expected strongest adverse effects in the south-eastern regions of Denmark with highest levels of PM_{2.5} due to strong contribution of long-range transported PM_{2.5} from central Europe (Fig. 1). Thus, overall, our findings do not provide strong support for relevance of any specific source of PM_{2.5} for mortality, and more data on source specific components of PM are needed to elucidate which

sources of PM_{2.5} are most relevant for mortality.

There are several strengths associated with our study. We benefited from having access to a large cohort with over 20 years follow-up for mortality and with detailed information on potential individual and contextual confounders. Moreover, a state-of-the-art high-resolution air pollution model provided historical estimates of air pollutants at the nurses' addresses, allowing modeling of time-varying effects of exposure. Another strength of our study is the ability to adjust for residential road traffic noise exposure, in the same resolution (3-year mean exposure at residence) as we examined associations with air pollutants.

Due to missing data on air pollution and individual risk factor data, we excluded a large portion of participants of the Danish Nurse Cohort for the analyses, and we cannot ignore the possibility of selection bias. Another limitation of this study is the potential misclassification, both in outcome and exposure. The validity of the cause of death registrations is a concern as some studies reported a pronounced discrepancy between the death certificates diagnoses and the eventual findings of an autopsy (Ravakhan, 2006; Sington and Cottrell, 2002). In 2005, the total autopsy rate in Denmark was 2.6%, 1% for those aged 60 years and older, and 11%, for those aged 40–59 years (Larsen and Lynnerup, 2011). Misclassification of exposure is likely since it was based only on outdoor levels at the façade of residence, and we lacked information on personal exposure during the time spent at home, work, and commuting.

5. Conclusion

In this Danish cohort of female nurses with up to 20 years of follow-up, long-term exposure to low-levels of PM_{2.5} was associated with increased risk of total, CVD, and diabetes mortality, independently of exposure to road traffic noise. Associations with total mortality were mainly driven by diabetes, hypertension, and IHD mortality. Associations with mortality were even more pronounced at PM_{2.5} levels below the EU limit values, adding to the evidence that more stringent air quality standards for PM_{2.5} would likely significantly reduce the death toll associated with air pollution, and supporting governments in introducing new measures to reduce exposure to air pollution.

CRediT authorship contribution statement

Rina So: Methodology, Software, Formal analysis, Visualization, Writing - original draft. **Jeanette Thørmø Jørgensen:** Resources, Data curation. **Youn-Hee Lim:** Validation, Writing - review & editing. **Amar J. Mehta:** Validation, Writing - review & editing. **Heresh Amini:** Visualization. **Laust H. Mortensen:** Resources, Data curation. **Rudi Westendorp:** Writing - review & editing. **Matthias Ketzl:** Resources, Data curation. **Ole Hertel:** Resources, Data curation. **Jørgen Brandt:** Resources, Data curation. **Jesper H. Christensen:** Resources, Data curation. **Camilla Geels:** Resources, Data curation. **Lise M. Frohn:** Resources, Data curation. **Torben Sigaard:** Writing - review & editing. **Elvira Vaclavik Bräuner:** Validation, Writing - review & editing. **Steen Solvang Jensen:** Resources, Data curation, Resources, Data curation. **Claus Backalarz:** Resources, Data curation. **Mette Kildevæld Simonsen:** Resources, Data curation. **Steffen Loft:** Writing - review & editing. **Tom Cole-Hunter:** Writing - review & editing. **Zorana Jovanovic Andersen:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing - original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.105983>.

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